TRAVERSAL OF RESTRICTION REQUIREMENT

The Office Action states that the previous Restriction Requirement is proper and made final. Applicant submitted a Petition under 37 C.F.R. §1.144 on August 16, 2002, *i.e.*, within two months of the mailing date of the instant Action, for reconsideration of the Restriction Requirement as between Groups I and IV, or alternatively as between Groups I and V, or alternatively as between Groups I and VI.

Applicant respectfully requests reconsideration of the Restriction Requirement in view of the following remarks. The Office Action, mailed on June 17, 2002, urged that the Restriction Requirement is based on the allegation that all of the groups presented, not just some of them, must be so linked as to have unity of invention. It is respectfully submitted that Groups I and IV, and Groups I and V, and Groups I and VI , do not lack unity of invention for the reasons set forth below, and therefore the restriction requirement in improper.

This application is the U.S. national stage of International Patent Application No. PCT/US98/02007, in accordance with 35 U.S.C. §371. As stated in MPEP 201, national stage applications of international applications are similar to national applications, but there are differences. Among these differences is inapplicability of restriction practice to national stage applications. Restriction practice is applied to national applications, but unity of invention practice is applied to national stage applications (see, MPEP 201 and MPEP 1893.03(d)).

Lack of Unity Standard

When the U.S.Patent Office considers an international application **during the national stage**, restriction must be based on unity of invention, which is governed by PCT Rule 13 (see MPEP 1893.03(d); Caterpillar Tractor Co. v. Commissioner of Patents and Trademark, 650 F. Supp. 218, 31 USPQ 590 (E.D. Virginia, 1986); In re Caterpillar Tractor Co, 228 USPQ 77). In the

Caterpillar cases it was ultimately held that the language in Rule 13.1 "specially adapted" is not to be interpreted as meaning that the process of manufacture can only be used to manufacture the product because this interpretation is in conflict with the PCT Rule, which provides that no national law shall require compliance with requirements relating to the form or contents of the international application different from or additional to those which are provided in the Treaty (Article 27 of the PCT). Thus, the U.S. Patent Office cannot impose requirements that differ from those provided in the Treaty. Since restriction practice differs from and is more restrictive than unity of invention, the unity of invention rules must govern.

Therefore, it is respectfully submitted, and it appears that the Office has acknowledged, that the rules of unity of invention (PCT Rule 13.1 and 37 C.F.R. §1.475) apply to this application. Rule 13.1 requires that an international application shall relate to one invention only or to a **group of inventions so linked as to form a single general inventive concept.**

PCT Rule 13

It is respectfully submitted that Groups I and IV, and Groups I and V, and Groups I and VI, relate to (i) a product and a process for the manufacture of said product (Group I), and (ii) a use of the said product (each of Groups IV, V and VI), and therefore do not lack unity of invention under PCT Rule 13. It is therefore respectfully requested that Groups I and IV, or alternatively Groups I and V, or alternatively Groups I and VI, be examined in the instant application.

Groups I and IV

Group I is directed to a composition and a method of preparing the composition. Group IV is directed to a method of purification using the composition of claim 44. Claim 44 is in Group I. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

> An international or a national stage application containing claims to different categories of invention will be considered to have unity of

> invention if the claims are drawn only to one of the following combinations of categories:
> ...
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product...

The claims of Group IV are directed to a use of the composition of Group I (a method of purification), and the claims of Group I are directed to a product and a process specially adapted for the manufacture of the product (a process for preparing the composition of claim 1). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups I and IV. In view of Applicant's election of Group I herein, it is respectfully requested that the claims of Groups I and IV, *i.e.*, claims 1-19, 44-49 and 53-56, be examined in the instant application.

Groups I and V

Group I is directed to a composition and a method of preparing the composition. Group V is directed to a method of sequencing using the composition of claim 44. Claim 44 is in Group I. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

> An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
> ...
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product...

The claim of Group V is directed to a use of the composition of Group I (a method of sequencing), and the claims of Group I are directed to a product and a process specially adapted for the manufacture of the product (a process for preparing the composition of claim 1). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups I and V. In view of Applicant's election of Group I herein, it is respectfully requested that the claims of Groups I and V, *i.e.*, claims 1-19, 44-47, 50 and 53-56, be examined in the instant application.

Groups I and VI

Group I is directed to a composition and a method of preparing the composition. Group VI is directed to a method of genetic or expression profiling using the composition of claim 44. Claim 44 is in Group I. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

> An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
> ...
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product...

The claim of Group VI is directed to a use of the composition of Group I (a method of genetic or expression profiling), and the claims of Group I are directed to a product and a process specially adapted for the manufacture of the product (a process for preparing the composition of claim 1). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups I and VI. In view of Applicant's election of Group I herein, it is respectfully requested that the claims of Groups I and VI, *i.e.*, claims 1-19, 44-47, 51 and 53-56, be examined in the instant application.

Summary

As noted above, applicant has submitted a Petition pursuant to 37 C.F.R. §1.144 that was timely filed within 2 months from the mailing of the Office Action requesting reconsideration of the Restriction Requirement as between Groups I and IV, or as between Groups I and V, or as between Groups I and VI.

In view of applicant's election of Group I, applicant respectfully requests that Groups I and IV, or alternatively, Groups I and V, or alternatively Groups I and VI, be examined in the instant application.

RIGHT OF PRIORITY TO U.S. APPLICATION NO. 60/037,165

The Office Action alleges that instant claims 1-28, 44-47, and 53-56 are not entitled to claim priority to provisional application 60/037,165. The Office Action alleges that claims 1-19, 44-47, and 53-56 are drawn to generic composition claims that encompass virtually any and all biopolymers, and in dependent claims, encompass virtually all the nucleic acids as well as antibodies. It is further alleged that the specification defines nucleic acids, enzymes, antibodies, etc., in terms of how they are to function, yet it does not provide an adequate written description of just what these compounds are. Further the Office Action has rejected claims 20-28 because they are allegedly drawn to a method of preparing the composition of claim 1. Applicant respectfully disagrees with the Examiner's conclusion.

Applicant respectfully submits that instant claim 1 is directed to compositions containing two biopolymers, where a first biopolymer is reversibly linked to a solid support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality. Dependent claims 2-19, 44-48, and 53-57 further define various components of the composition. Claims 20-28 are directed to methods of preparing composition of claim 1.

The claimed composition of instant claim 1 is described in claim 1 of the provisional application which is directed to a method to immobilize biopolymers on polymeric supports conjugated by one or more reversible linkages. The specification of the provisional application describes exemplary compositions on page 2, lines 27-34, and in Figures 1 (a) and (c), in which a spacer molecule linked to a polymer support forms a reversible linkage to a nucleic acid or

protein/peptide molecule which is linked by another reversible linkage to either a nucleic acid, protein/peptide or small molecule. The provisional application describes various components of the claimed compositions, for example, biopolymers are described in the specification on page 5, lines 9-25, the solid supports are described on page 4, lines 1-9, and reversible linkages are described on page 5, line 11 and page 5, line 27 through page 7, line 18, where exemplary reversible linkages, including heterobifunctional trityl, photocleavable, chelate, hydrophobic interaction, are described. Thus, the provisional application provides adequate written description for the claimed subject matter. Therefore, the application is clearly entitled to the benefit of priority.

Rebuttal to Specific Arguments in the Office Action

1. The Office Action alleges that claims 1-19, 44-47, and 53-56 are drawn to generic composition claims that encompass virtually all nucleic acids as well as antibodies. It is further alleged that the specification defines the nucleic acid in terms of how it is to function, as it does enzymes, antibodies etc., yet it does not provide an adequate written description of just what these compounds are. Applicant respectfully submits that the instant claims are not directed to any specific nucleic acids, enzymes or antibodies, but are directed to particular linked arrangements of biopolymers. Therefore there is no need to define what the specific compounds are since any biopolymer is contemplated for use in the claimed compositions. Moreover, the provisional application defines nucleic acids on page 5, lines 16-19, as

> either DNA or RNA single or double stranded, DNA/RNA hybrids, DNA containing ribonucleotides and/or deoxyribonucleotides and RNA containing deoxyribonucleotides, containing modified nucleotides as well as nucleic acid mimetics such as PNA.

The specification recites on page 5, lines 20-25,

> the terms "protein", "polypeptide" or "peptide" are all used interchangeably to refer to gene products. Proteins can be antibodies , enzymes, receptor molecules; peptides could be of natural or synthetic origin with oligo-his tail, a functionality for hydrophobic interaction, a photoclevable functionality or chelate functionality and displaying

different properties such as being adhesive or representing specific ligand-receptor or specific protease cleavage sites.

Therefore the provisional application provides an adequate written description of the compounds for use in the claimed compositions.

2. The Office Action further alleges that it is not enough that alternative embodiments may be obvious in light of the disclosure when coupled with what is known in the art, the specification must provide an adequate written description of the invention. Applicant respectfully submits that the allegation that alternative embodiments may be obvious in light of the disclosure when combined with the art, is irrelevant because as discussed above, all the embodiments are fully disclosed in the specification and the specification provides an adequate written description of the claimed subject matter.

REJECTION OF CLAIMS 1-28, 44-47, AND 53-56 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-28, 44-47, and 53-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action urges that claims 1-19, 44-47, and 53-56 are drawn to compositions that are comprised of biopolymers which are further defined in dependent claims as enzymes, nucleic acids (DNA, RNA, analogs or mimetics of DNA or RNA), antibodies, and polypeptides, and that these biopolymers are bound to various supports, be it inorganic, insoluble, magnetic, etc., and that there are various reversible linkages used to bind the biopolymers to the supports. The Office Action further alleges that the aspect

of defining a biopolymer as being a nucleic acid (including DNA, RNA, analogs or mimetics of DNA or RNA), as well as being a polypeptide etc., does not satisfy the written description requirement. Applicant respectfully traverses this rejection.

Relevant Law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description, has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the

subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

The guidelines promulgated by the U.S. PTO embody these rules:

> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
>
> (1) identify the claim limitation not described; and

> (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

in this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

The Instant Claims

Claim 1 is directed to compositions containing two biopolymers, where a first biopolymer is reversibly linked to a solid support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality. Dependent claims 2-19, 44-47, and 53-56, further define various components of the composition.

Analysis

Applicant respectfully submits that the instant claims are not directed to specific biopolymers but are directed to particular linked arrangements of biopolymers. Non-limiting examples of the claimed compositions are disclosed in Figures 1 (a)-(c) and on page 2, lines 27-34, of the priority application, and Figures 1 (a)-(c); page 2, lines 20-23; page 3, lines 14-21; and page 5, lines 12-15, of the PCT application, upon which this national phase application is based. An exemplary composition is pictorially depicted in Figure 1 in which a spacer molecule, A, linked to a polymer support, P, forms a reversible linkage, I, to a nucleic acid or protein/peptide molecule, B, which itself is linked by another reversible linkage, II, to either a nucleic acid, protein/peptide or small molecule (e.g. reporter molecule). The specification describes and exemplifies all the components of the claimed composition including the biopolymers (see *e.g.*, page 5, lines 12-16; page 6, lines 1-4; and page 7, line 18 through page 8, line 9); various solid supports for use in the claimed compositions (see *e.g.*, page 5, lines 17-26) and the reversible linkages (see, *e.g.*, page 3, lines 18-20; page 7,

lines 19-20; page 8, lines 13-15 and 21-27; and page 9, lines 1-18). The specification provides non-limiting examples where claimed compositions are used in the Ligase Chain Reaction and Polymerase Chain Reaction.

Since the specification discloses compositions containing two biopolymers, where a first biopolymer is reversibly linked to a solid support and a second biopolymer is reversibly linked to the first biopolymer, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality, and each of the components in the composition are described in the specification as discussed above, there is no basis to conclude that applicants did not have possession of the claimed subject matter at the time of filing of the application.

Rebuttal to Specific Arguments in the Office Action

1. The Office Action alleges that the aspect of defining a biopolymer as being a nucleic acid (including DNA, RNA, analogs or mimetics of DNA or RNA), as well as being a polypeptide etc., does not satisfy the written description requirement.

Applicant respectfully submits that, as discussed above, instant claim 1 is not directed to any specific nucleic acids, enzymes or antibodies, but are directed to particular linked arrangements of biopolymers. Therefore, there is no need to define what the specific compounds are since any biopolymer is contemplated for use in the claimed compositions. Moreover, biopolymers are described in the specification on page 5, lines 14-15, as organic molecules, including nucleic acids, peptides and polypeptides. Nucleic acids of the instant claims are further defined on page 7, line 25, through page 8, line 3,

> For use in the instant process, nucleic acids can be single stranded or double stranded polynucleotides (including oligonucleotides), whether natural or synthetic, such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) or DNA/RNA hybrids, DNA containing ribonucleotides and/or dideoxyribonucleotides and RNA containing deoxyribonucleotides. Also encompassed by the term "nucleic acid" are modified nucleotides (e.g.

> phosphorothioate modified) as well as nucleic acid mimetics or analogs, such as peptide nucleic acids (PNAs).

The specification on page 8, line 4-9, describes the terms "protein", "polypeptide" or "peptide",

> As used herein, the terms "protein", "polypeptide" or "peptide" are all used interchangeably to refer to gene products. Proteins can be antibodies, enzymes, receptor molecules; peptides could be of natural or synthetic origin with oligo-his tail, a functionality for hydrophobic interaction, a photocleavable functionality or chelator functionality and displaying different properties such as being adhesive or representing specific ligand-receptor or specific protease cleavage sites.

Therefore, the biopolymers for use in the claimed compositions are adequately described in the application.

2. The Office Action further alleges that it is not enough that certain undisclosed embodiments may be obvious when the disclosure is coupled with what was known in the art at the time of filing, the specification must provide an adequate written description of the invention and for the purposes of examination, the invention is what ever is being claimed.

Applicant respectfully submits that the allegation that certain embodiments may be obvious when the disclosure is combined with the art, is irrelevant because as discussed above, all the embodiments are fully disclosed in the specification and the specification provides an adequate written description of the claimed subject matter.

REJECTION OF CLAIMS 6 AND 7 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 6 and 7 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of compositions where all or "even some" of the claimed elements of the insoluble support are combined. The Office Action notes that an insoluble support is defined in claim 6 as being selected from a group consisting of flat surface, a microtiter plate, a comb, and a bead. It is noted that the supports are further defined in claim 7 as being a silicon wafer, glass plate, metal, plastic, film, and composites thereof with pits

or wells which are further defined as comprising inorganic material selected from the group consisting of silica, controlled pore glass(CPG), plastic, metal, cellulose, agarose and dextran cross-linked with epichlorohydrin. The Office Action alleges that a bead of some undisclosed type is contemplated for use in example 3 and that the suggestion in prophetic example does not reasonably suggest that applicant was in possession of the genus of compositions now being claimed. Applicant respectfully traverses this rejection.

Relevant Law

As discussed above.

Instant Claims

Claim 6 defines insoluble supports as being selected from a group consisting of flat surface, a microtiter plate, a comb, and a bead. The insoluble supports are further defined in claim 7 as being a silicon wafer, glass plate, metal, plastic, film, and composites thereof with pits or wells. Claims 8-10 further define the insoluble supports.

Analysis

Applicant respectfully submits that the "insoluble supports" are described in the specification on page 5, lines 17-26. The specification discloses:

> the insoluble supports can be flat such as membranes, glass plates, metals, plastic films and composites thereof with a homogeneously functionalized surface or functionalized to result in an array format including flat supports with pits, wells, combs, microtiter plates, microtiter filter plates; flat supports can also be magnetic or with an array shaped (checkered) magnetic field; solid supports can also be used as beads from different plastic materials, inorganic supports such as silica, GPG (Controlled Pore Glass), metal, different polymeric material, cellulose, Sephadex, Sepharose; the beads can be porous or non-porous, of different diameter and magnetic or non-magnetic. Also a combination of beads in the pits/wells of flat supports thus forming an array format can be employed.

Claims 6-10 in the priority application as well as PCT application as originally filed, disclose the subject matter of the instant claims. For example, see below:

6. A composition according to claim 1, wherein the insoluble support is selected from the group consisting of: a flat surface, a comb and a bead.

7. A composition according to claim 6, wherein the insoluble support is selected from the group consisting of: a silicon wafer, glass plate, metal, plastic, film and composites thereof with pits or wells.

8. A composition according to claim 7, wherein the biopolymer is conjugated to the insoluble support in an array format.

9. A composition according to claim 7, wherein the bead is comprised of an inorganic material selected from the group consisting of: silica, Controlled Pore Glass (CPG), plastic, metal, cellulose, Sepharose and Sephadex.

10. A composition according to claim 6, wherein the insoluble support is comprised of a magnetic or electromagnetic material.

The specific examples recite exemplary insoluble supports such as beads (See page 15, example 2), microtiter filter plates with wells (See page 15, example 3) and a membrane derivatized with a capture oligo (See page 16, example 4). Thus, the application as originally filed discloses the genus of composition for the claimed insoluble supports.

The Examiner is reminded that possession may be shown by describing actual reduction to practice of the claimed subject matter and filing of a patent application is a reduction to practice (M.P.E.P.§ 2163). Also, possession does not mean physical possession but appreciation. Therefore, the specification provides adequate written description where all of these requisite elements are combined and there is no basis to conclude that the applicant was not in possession of the genus of compositions being claimed.

Rebuttal to Specific Arguments in the Office Action

The Office Action alleges that a bead of some undisclosed type is contemplated for use in example 3 and that the suggestion in prophetic example

does not reasonably suggest that applicant was in possession of the genus of compositions now being claimed.

Applicant respectfully submits that the allegation that the suggestion in prophetic example does not reasonably suggest that applicant was in possession of the genus of compositions now being claimed is irrelevant because the application as originally filed discloses the genus of composition for the claimed insoluble supports and examples are not required to satisfy a written description requirement. Furthermore, as discussed above, specific examples in the application recite exemplary insoluble supports and claims 6-10 as originally filed, disclose the genus of compositions being claimed.

REJECTION OF CLAIMS 20-28 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 20-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not set forth in sufficient detail the method of claims 20-28, whereby one is to produce the compositions encompassed by claim 1. The Office Action notes that the claimed method requires one to utilize various first and second reversible linkages formed through a trityl derivative, chelate complex, a hydrophobic interaction or a photocleavable functionality. It is further noted that other claims require that an enzymatic process is used to introduce functionalities into nucleic acids and that this enzymatic process is part of a nucleic acid sequencing reaction. The Office Action alleges that a review of the specification fails to find where such methods are described even in the context of a prophetic example. The Office Action further alleges that the examples and guidance provided is found, at best, to only indirectly suggest or make obvious the claimed methods and that it does not satisfy the written description requirement. Applicant respectfully disagrees.

Relevant Law

As discussed above.

The Instant Claims

Claim 20 depends from claim 1 and is directed to producing the composition of claim 1 containing two biopolymers, where a first biopolymer is reversibly linked to a solid support and a second biopolymer is reversibly linked to the first biopolymers, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality. Claim 21 and 22 further define the reversible linkages. Claims 23-28 further describe introduction of functionalities into the biopolymers to form the reversible linkages.

Analysis

Compositions produced by the claimed methods comprising various first and second reversible linkages formed through, for example, a trityl derivative, chelate complex, a hydrophobic interaction or a photocleavable functionality, are described in the specification as discussed above (see e.g., Figures 1 (a)-(c); page 2, lines 20-23; page 3, lines 14-21; page 5, lines 12-15; and page 6, lines 1-8 and lines 15-24). An exemplary method where an exemplary composition is prepared utilizing reversible linkages formed through a chelate complex between chelator functionality, for example, nitriloacetic acid (NTA) which coordinates with divalent metal cations such as Ni^{2+} and forms a strong complex with six imidazolyl groups from a his_6 tail linked to one of the conjugating partner molecules is described in the specification (see, figure 4; specification page 9, lines 19-25). Introduction of his_6 tail in Bacterial Alkaline Phosphatase (BAP) via inverse PCR is disclosed in the specification on page 11, lines 1-16, and on page 14, Example 1. Functionalization of nucleic acid molecules with imidazolyl or chelator functionalities is described on page 11, line 21, through page 12, line 25. Enzymatic processes for introduction of the chelator or imidazolyl functionalities in the nucleic acid during amplification procedures such as PCR,

SDA or during DNA sequencing are disclosed in figures 11-12, and specification page 12, lines 14-25.

Thus the claimed methods are fully disclosed in the specification. Therefore, the allegation that the examples and guidance provided is found, at best, to only indirectly suggest or make obvious the claimed methods is improper.

REJECTION OF CLAIMS 1-28, 44-47, AND 53-56 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-28, 44-47, and 53-56 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that aside from providing an adequate written description of the invention, the specification must also enable the use of the invention. The Office Action alleges that as presently worded the claims encompass a vast multitude of compositions yet the specification does not set forth in sufficient detail just how one is to differentiate between those embodiments that work and those that will not work. It is further alleged that the specification does not teach in sufficient detail how to use the multitudinous compositions disclosed in the specification, in any of the claimed methods, much less enable all the compositions in all the methods. Applicant respectfully traverses this rejection.

Relevant Law

It is incumbent upon the examiner to first establish a prima facie case of non-enablement. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first

> paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.)

Id. (emphasis in original); See also Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, Gould v. Mossinghoff, 229 USPQ 1, 13 (D.D.C. 1985), aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct").

In order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of

experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect to scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to

whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

The Instant Claims

Claim 1 is directed to a composition, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality.

Dependent claims 2-4, 11, 12, 17-19, 44, and 53-56 further define the biopolymers. Dependent claims 5, 8, 13-16, 45, and 56 further define the reversible linkages. Dependent claims, 6, 7, 9, 10, and 45-47 further define the insoluble support. Claims 20-28 are directed to methods for preparing the claimed compositions.

Analysis

Applying the above factors to the instant claims, applicant respectfully submits that, as described in detail below, it would not require undue experimentation to practice the full scope of the claimed subject matter.

Scope of the claims

The compositions in the instant application contain specific elements that are described and taught in the specification. Various linked arrangements of biopolymers in the claimed compositions are exemplified, for example, in Figures 1-3. The specification defines all the components in the compositions, for example, biopolymers are defined on page 5, lines 12-16, as organic molecules, including nucleic acids, peptides and polypeptides; various insoluble supports for use in claimed compositions are described in the specification (see page 5, lines 17-26); exemplary reversible linkages are disclosed in the specification and include heterobifunctional trityl groups, hydrophobic interactions stable under aqueous conditions, photocleavable bonds, and chelate complexes (see, *e.g.*,

page 3, lines 18-20, page 4, lines 3-4, page 8, lines 13-15 and 21-27, and page 9, lines 1-18). The specification, including the working examples, describes how to make the compositions. Therefore claims 1-28, 44-47 and 53-56 are directed to compositions and methods for preparing these compositions, that are described in the specification. Thus the instant claims are not overly broad as compared to the scope of the disclosure.

The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew the use of reversibly linking biopolymers in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry as evidenced by a large body of literature directed to the use of reversibly linked biomolecules.

The articles cited in the specification, of record and attached hereto, describe reversible linkages and their uses in various applications. For example, use of reversibly linked biomolecules in DNA sequencing is disclosed in WO 96/29431. The patent describes the use of photocleavable bond such as a charge transfer complex or a labile bond formed between relatively stable organic radicals as reversible linkages in DNA sequencing.

U.S Patent No. 5,410,068, describes reversible immobilization of compounds with a triphenylmethyl group as a linking agent for use in polymerase catalysed extension reaction.

Leikauf *et al.*, *Tetrahedron*, **1995**, 51(13), 3793-3802, describes use of heterobifunctional trityl derivatives as reversible linking agents for the recovery of nucleic acids after labeling and immobilization.

Blum *et al.*, *J. Biochem. Biophys. Methods*, **1994**, 29, 113-121, have reported the use of reversible linkage in enzyme purification.

Hochuli *et al.*, *Methods: A Companion to Methods in Enzymalogy*, **1992**, 4, 68-72, have reported the use of reversible linkage formed through chelate complex in affinity purification of proteins.

Smith *et al.*, *The J. Biol. Chem.*, **1988**, 263 (15), 7211-7215, have described purification of proteins using reversible linkages.

Köster *et al.* in WO 96/29431, have disclosed the use of reversible linkers in DNA diagnostics.

The use of reversible linkers in DNA sequencing is disclosed in WO 94/21822.

In addition, a large body of publications, not cited in the application, describe the use of reversible linkages in various applications.

Scoten *et al.*, *Anal. Biochem.*, **1992**, 205, 313-18, have described reversible immobilization in solid phase biotechnology.

Penke et al. *J. Chroma.*, **1986**, 376, 307-314, have reported reversible linkages for targeted immobilization of Neurotransmitters and Neuropeptides.

Kadonaga *et al.*, *Biochemistry*, **1986**, 83, 5889-5893, have used reversible linkers in affinity purification of sequence specific DNA binding proteins.

Cuatrecasas *et al.*, *Biochemistry*, **1968**, 61, 636-643, have used reversible linkers in enzyme purification by affinity chromatography.

Köster *et al.* in U.S.patent 5,948,624, have disclosed use of reversible linkers in DNA sequencing.

U.S. Patent No. 5,547,835 discloses several examples of functionalities that can form charge transfer complexes and thereby form reversible linkages for use in DNA sequencing.

Gildea *et al.*, *Tetrahedron*, **1990**, 31, 7095-98, have reported triphenylmethyl protecting group as a reversible linker for purification and analysis of chemically and enzymatically synthesized nucleic acids.

Hence, those of skill in the art are well- aware of various uses of reversibly linked biomolecules in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry. Based on the teachings and guidance in specification and the knowledge of those of skill in the art, one can readily select those compositions that are used in these contemplated methods.

The amount of direction and guidance presented, teachings in the specification and presence of working examples

The specification describes the claimed compositions as discussed above. The two biopolymers are further described in the specification e.g., page 5, lines 14-16; insoluble supports are described at, e.g., page 5, lines 17-26; and reversible linkages are defined at, e.g., page 7, lines 19-20, page 8, lines 13-15 and 21-27, page 9, lines 1-18. Exemplary use of the claimed compositions in Ligase Chain Reaction (LCR) and Polymerase Chain Reaction (PCR) is illustrated in the specification on page 15, Example 3 (Figure 13); and page 16, Example 4 (Figure 14), respectively. Numerous articles cited in the application and attached hereto teach the use of the claimed compositions in DNA sequencing, DNA diagnostics, nucleic acid amplification, Polymerase and Ligase Chain Reactions (PCR, LCR), hybridization experiments and solid phase biochemistry. Therefore, the application provides sufficient guidance for one of skill in the art to make and use the full scope of the claimed subject matter.

CONCLUSION

In light of the scope of the claims, the description in the application, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation to make and use the full scope of the claimed compositions and methods. Therefore, the specification is enabling for the full scope of the claimed compositions and methods.

REJECTION OF CLAIMS 1-14 UNDER 35 U.S.C. §102(e)

Claims 1-14 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Köster *et al.* (U.S. Patent No. 6,225,450 B1). The Office Action urges that this reference allegedly discloses the immobilization of biopolymers such as nucleic acids to the solid support wherein the biopolymers are reversibly bound to the solid supports. The Office Action further states that Köster *et al.* discloses suitable supports. Applicant respectfully traverses this rejection.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ

USPQ 323, 326 (CCPA 1981). "Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter *is* identically disclosed or described in the "'prior art'" "...the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection." [Emphasis in original]. *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA 1972).

Instant claims 1-14

Claims 1-14 are directed to compositions, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage.

Differences between the disclosure of Köster *et al.* and instant claims

Köster *et al.* disclose reversible immobilization of biopolymers such as nucleic acids to a solid support wherein the biopolymers are reversibly bound to the solid support through a linker. See column 11, lines 52-56:

> nucleic acid primer that carries a linking functionality, L, which can include a spacer of sufficient length and which can interact with a suitable functionality, L', on a solid support to form a reversible linkage such as a photocleavable bond.

Köster *et al.* does not disclose the claimed compositions because it does not disclose a second biopolymer bound to a first biopolymer by a reversible linkage, as claimed in the instant application. Therefore, the disclosure of Köster *et al.* does not anticipate the instant claims.

REJECTION OF CLAIMS 1-14 UNDER 35 U.S.C. §102(f)

Claims 1-14 are rejected under 35 U.S.C. §102(f) because the applicant allegedly did not invent the claimed subject matter. The Office Action alleges that '450 patent to Köster lists a single inventor yet it describes the invention of claims 1-14.

Relevant Law

As discussed above.

Instant Claims 1-14

Claims 1-14 are directed to compositions, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage.

Analysis

Applicant respectfully submits that a rejection under 35 U.S.C. § 102(f) is proper only when it can be shown that the Applicant derived an invention from another. M.P.E.P. § 2137. "Derivation requires complete conception by another and communication of that conception by any means to the party charged with derivation . . . ." M.P.E.P. § 2137.

As discussed above, the Köster patent does not disclose the claimed compositions, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage. Therefore, there is no basis for an inference of improper inventorship.

REJECTION OF CLAIMS 1-14 UNDER 35 U.S.C. §102(e)

Claims 1-14 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Rothschild *et al.* The Office Action states that this reference discloses the development and wide application of photocleavable biotin (PCB). The Office Action further urges that PCB can be used to form conjugates with an extremely wide variety of biopolymers, including polypeptides, nucleic acids,

etc. A plethora of applicable solid supports, including insoluble supports are disclosed at column 25. The Office Action alleges that the aspect of having complexes formed off of the conjugated biopolymer whereby one biopolymer is used to bind to yet another biopolymer is disclosed throughout the cited reference. Applicant respectfully traverses this rejection.

The relevant law

As discussed above.

Instant claims 1-14

Claim 1 is directed to a composition, comprising two biopolymers, wherein, the first biopolymer is linked to an insoluble support by a reversible linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality. Dependent claims 2-13 further describe the biopolymers, the reversible linkages and the solid supports.

Differences between the disclosure of Rothschild *et al.* and instant claims

Rothschild *et al.* discloses methods for isolation and detection of biomolecules wherein photocleavable biotin is used to form conjugates with biomolecules. Exposure of the conjugate to electromagnetic radiation releases the biomolecule in an unaltered form. Rothschild *et al.* does not disclose a composition containing two biopolymers, where the first biopolymer is linked to an insoluble support by a reversible linkage and the second biopolymer is bound to a first biopolymer by a reversible linkage, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality, as claimed in the instant application. Thus, Rothschild *et al.* does not disclose all elements as claimed. Therefore, the disclosure of Rothschild *et al.* does not anticipate the instant claims.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie Seidman
Registration No. 33,779

Attorney Docket No. 24736-2303US
Address all correspondence to:
Stephanie Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122
Telephone: 858/450-8400
Facsimile: 858/587-5360
email: sseidman@HEWM.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*
Serial No.:	09/355,705
Confirmation No.:	6820
Filed:	November 5, 1999
For:	A REVERSIBLE STOICHIOMETRIC PROCESS FOR CONJUGATING BIOMOLECULES
Art Unit:	1634
Examiner:	Sisson Bradley L.

ATTACHMENTS TO THE AMENDMENT

The following attachments are provided:

(1) Marked up paragraphs and claims in accordance with 37 CFR §1.121; and

(2) a Supplemental Information Disclosure Statement.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*
Serial No.:	09/355,705
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MARKED UP CLAIMS (37 CFR §1.121)

Please amend claims 1 and 21 as follows:

1. (Amended Three Times) A composition, comprising two biopolymers, wherein:

the first biopolymer is linked to an insoluble support by a reversible linkage; and

the second biopolymer is linked to the first biopolymer by a reversible linkage, wherein the linkage between the first biopolymer and the second biopolymer is formed through a trityl derivative, a chelate complex or a photocleavable functionality.

21. (Amended Three Times) The method of claim 20, wherein the first [or second] reversible linkage is formed through a trityl derivative, a chelate complex, a hydrophobic interaction or a photocleavable functionality and the second reversible linkage is formed through a trityl derivative, a chelate complex or a photocleavable functionality.